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## **A Novel Cytomegalovirus-Initiated Signal Pathway**

**[Purification and identification of human cytomegalovirus activated proteins involved in a novel viral-mediated signal transduction pathway.]**

Human cytomegalovirus (CMV) is a ubiquitous human pathogen. It is a major cause of morbidity and mortality in immunocompromised individuals, especially in transplant recipients and AIDS patients. CMV infection is also a leading cause of birth defects. Severe CMV infections occur in transplant recipients. Studies in small animal models and cell culture systems support the role of CMV infection in the development of heart diseases. Many studies have shown that CMV infection has important impact on cancer patients and it is a possible co-factor in tumor genesis.

My long-term research goal is to understand how CMV causes diseases in the human host. We have discovered that interferon-stimulated genes are turned on upon CMV infection. This pathway is distinct from the normal one used by interferons to activate these genes. In addition, a key cis-acting element, the  $\gamma$ -interferon activation site (GAS) is present in both transcriptional promoters of interferon-stimulated genes and CMV major immediate early genes. By identifying the viral-activated protein(s) that bind to both the GAS elements in the host interferon-stimulated genes and the CMV immediate early genes, we can begin to unravel this novel pathway. Our investigations will be accomplished by:

- 1) **Identifying GAS element binding proteins.** The GAS element, located within the promoters of interferon-stimulated genes, responds to CMV infection by upregulating gene transcription. We will purify these GAS-binding protein(s) by conventional chromatography and identify them using mass spectrometric analysis.
- 2) **Determining the function of these GAS-binding proteins in CMV infection.** After identification of the proteins that interact with the GAS elements, we will determine their role in viral infection, using *in vivo* protein/DNA crosslinking and cellular localization patterns.

In this application we have detailed experiments designed to elucidate the molecular mechanism of a novel CMV-mediated signal pathway and its actual role CMV replication. This work will lead to a clearer understanding of the pathogenesis CMV-related diseases.